Sleep Research Review™

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Issue 15 - 2025

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Abbreviations used in this issue:

AHI = apnoea-hypopnoea index;
AHPRA = Australian Health Practitioner Regulation Agency;
CPAP = continuous positive airway pressure;
GIP = glucose-dependent insulotropic polypeptide;
GLP-1 = glucagon-like peptide-1; **HR** = hazard ratio;
IBD = inflammatory bowel disease; **MACE** = major adverse cardiovascular events;
OSA = obstructive sleep apnoea; **RLS** = restless legs syndrome;
T2D = type 2 diabetes.

Welcome to the latest issue of Sleep Research Review.

In this issue, the findings of a Spanish study suggest that CPAP may have a protective effect on blood pressure in normotensive patients with severe OSA, US investigators use sleep apnoea-specific hypoxic burden to assess the benefits of a mandibular advancement splint in OSA, and an analysis of the European READ-ASV Registry suggests that adaptive servo-ventilation therapy may be beneficial in opioid users with sleep-disordered breathing.

We hope you find these and the other selected studies interesting, and look forward to receiving any feedback you may have.

Kind regards,

Dr Elizabeth Veitch
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Comparative efficacy of tirzepatide, liraglutide, and semaglutide in reduction of risk of major adverse cardiovascular events in patients with obstructive sleep apnea and type 2 diabetes: Real-world evidence

Authors: Henney AE et al.

Summary: This real-world study compared the effects of the GLP-1/GIP receptor agonist tirzepatide and the GLP-1 agonists liraglutide and semaglutide on MACE in patients with OSA and T2D. Two cohorts were generated from a large global database of patients with OSA and T2D. Each cohort had a treatment arm (tirzepatide) and a propensity-score matched reference arm (liraglutide in cohort 1 and semaglutide in cohort 2). A total of 7836 patients were enrolled in each arm in cohort 1 and 7394 patients were enrolled in each arm in cohort 2. Overall, tirzepatide reduced the risk of incident MACE compared with liraglutide (HR 0.58, 95% CI 0.51–0.66) and semaglutide (HR 0.86, 95% CI 0.74–0.99), and reduced incident OSA compared with liraglutide (HR 0.89, 95% CI 0.82–0.97) but not semaglutide (HR 0.94, 95% CI 0.86–1.02).

Comment: T2D and OSA are independent risk factors for cardiovascular disease. The treatment of T2D and obesity has been transformed by the development of potent glucose- and weight-lowering drugs, including the GLP-1 receptor agonists semaglutide and liraglutide, and the GLP-1/GIP receptor agonist tirzepatide. Several large trials have proven the benefit of these drugs in treating OSA, but the primary outcomes were AHI reduction. This retrospective cohort study examined their impact on MACE in patients with T2D and OSA. Over an 18-month period tirzepatide proved superior to liraglutide with respect to composite MACE and each cardiovascular event independently, with the exception of sudden cardiac death, and it showed a trend to superiority over semaglutide. This suggests superiority of GLP-1/GIP receptor agonists in reducing cardiovascular morbidity in high-risk groups, though prospective trials are needed to confirm this.

Reference: Ann Am Thorac Soc. 2025;22(7):1042–52
Abstract

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Effect of continuous positive airway pressure on blood pressure in normotensive individuals with obstructive sleep apnoea

Authors: Targa ADS et al.

Summary: This randomised controlled trial in Spain investigated the impact of CPAP on blood pressure (BP) in normotensive patients with a "dipping" BP pattern and severe OSA. Sixty patients (mean 52.2 years, 66.7% male) with AHI ≥30 events/h, mean 24-h BP <130/80mm Hg and a daytime to night-time BP fall of ≥10% were randomised to receive either CPAP treatment or usual care for 12 weeks. The intention-to-treat analysis showed no significant BP changes in the CPAP group at 12 weeks, whereas the usual care group had an increase in night-time diastolic BP (p=0.015). The per-protocol analysis found significant differences between the CPAP and usual care groups for all ambulatory BP measures.

Comment: In healthy individuals BP follows a circadian rhythm, with falls of 10–20% during sleep ("dipping"). Abnormalities in this rhythm, such as "non-dipping" overnight, are associated with adverse cardiovascular outcomes. Patients with OSA experience heightened sympathetic activation during sleep, which is associated with the initiation and progression of hypertension. The use of nocturnal CPAP in hypertensive OSA patients assists in reducing nocturnal and 24-h BP, but its impact in normotensive individuals is unclear. This study investigated CPAP in OSA patients with normal daytime BP and a continued physiological pattern ("dipping"). Unfortunately, small study numbers, exacerbated by inadequate CPAP adherence in 26% of patients, impacted on the trial result, with no differences in intention-to-treat analysis, although per-protocol analysis found significant improvements in daytime and night-time BP. Thus, a protective effect of CPAP in preventing BP increases in normotensive OSA patients is suggested, with larger trials needed to confirm this.

Reference: Eur Respir J. 2025;66(1):2401954
Abstract

Oral appliance therapy is highly efficacious at reducing sleep apnea-specific hypoxic burden, a metric predictive of cardiovascular morbidity and mortality

Authors: Mosca EV et al.

Summary: Sleep apnoea-specific hypoxic burden (SASHB) is a surrogate measure of cardiovascular risk in patients with OSA. This prospective observational study in the US used SASHB and AHI to evaluate the therapeutic efficacy of a mandibular oral appliance in 152 individuals with mild, moderate, or severe OSA. Two-night home sleep apnoea tests were used to determine AHI and SASHB at baseline and when using the oral appliance. Mean baseline SASHB differed by OSA severity, with 0%, 19%, and 94% of patients with mild, moderate, and severe OSA, respectively, having values >60% min/h. When using the oral appliance these values decreased to 0%, 0%, and 15%, respectively. Overall, therapeutic efficacy was 78% when AHI <10 events/h was used as the outcome measure and 95% when SASHB <60% min/h was used as the outcome measure.

Comment: Mandibular advancements splints (MAS) have long been regarded as the 'poor cousin' of OSA therapy, failing to achieve the normalisation of AHI seen with nocturnal positive airway therapy. However, recent studies have shown that SASHB, not AHI, predicts increased cardiovascular morbidity and mortality in OSA, suggesting that this may be the more important parameter to normalise. This trial assessed the impact of one MAS (ProSomnus®) across a range of OSA severity, finding better OSA control based on SASHB than AHI. The study has its flaws – it was a re-analysis of data from prior studies (two published, one unpublished), included no information on symptom assessment or device tolerability, and was conducted by the makers of the ProSomnus® MAS. However, it is the first oral appliance study to use SASHB as the main outcome measure and proves that this particular MAS is efficacious in controlling SASHB.

Reference: J Clin Sleep Med. 2025;21(7):1185–90
Abstract

Effect of an overnight stay at 2,500 meters on nocturnal hypoxemia and sleep-disordered breathing in patients with pulmonary vascular disease

Authors: Lichtblau M et al.

Summary: This randomised crossover trial investigated the effects of high altitude on nocturnal hypoxaemia and sleep apnoea in patients with pulmonary vascular disease. Twenty-seven patients (mean age 62 years) with pulmonary arterial hypertension (PAH) or chronic thromboembolic pulmonary hypertension underwent respiratory polygraphy at an altitude of 470m and again during an overnight stay at 2500m. Overall, 10 (37%) patients with severe hypoxaemia (oxygen saturation [SpO_2] <80% for >30 min) at 2500m received supplemental oxygen therapy according to safety criteria. At 470m versus 2500m, mean nocturnal SpO_2 was 91% versus 83% (p<0.001), time with SpO_2 <90% was 29 min versus 92 min (p<0.001), and oxygen desaturation index was 17 events/h versus 42 events/h (p<0.001). AHI did not differ between 470m and 2500m. When required, supplemental oxygen therapy restored SpO_2 levels to those seen at 470m.

Comment: PAH is incurable but therapeutic advances in the last 20 years have markedly increased the survival of these patients. Hypoxaemia is known to cause pulmonary vasoconstriction, which can potentially exacerbate pulmonary hypertension. Furthermore, PAH patients have been reported to have an increased rate of OSA and central sleep apnoea. Not surprisingly this trial found significant increases in hypoxaemia and oxygen desaturation index when patients with pulmonary vascular disease slept at high altitude, however the AHI was not affected. A minority of patients required supplemental oxygen, but this need could not be predicted by standard clinical variables. The consequences of nocturnal hypoxaemia in this patient group remain unclear and warrant further investigation.

Reference: Ann Am Thorac Soc. 2025;22(7):1053–61
Abstract

Treatment of sleep-disordered breathing in opioid users with adaptive servo-ventilation

Authors: Pepin J-L et al., for the READ-ASV Investigators

Summary: This subgroup analysis of the European READ-ASV Registry investigated the effects of adaptive servo-ventilation (ASV) therapy on sleep-disordered breathing (SDB) symptoms in opioid users. Eighty-six patients who reported opioid use and were initiated on ASV were followed up for 12 months. The population had severe SDB (median AHI 55 events/h), 87% of them had comorbidities, and 81.6% were symptomatic at baseline. ASV effectively improved SDB (residual median AHI was 1.5 events/h). The Functional Outcomes of Sleep Questionnaire score (+1.4 points; p=0.003) and the Epworth Sleepiness Scale score (–3 points, p=0.029) also improved significantly from baseline at 12 months.

Comment: Central sleep apnoea (CSA) occurs due to a lack of respiratory drive or instability in respiratory control. Heart failure is the leading cause of CSA, with opioid use coming second. The proportion of people on opioids who develop CSA ranges in prior studies from 20–60% and symptoms of this can be difficult to differentiate from opioid adverse effects. Thus, the American Academy of Sleep Medicine recommends screening for SDB in patients requiring long-term opioids. This study examined patients from the READ-ASV Registry who reported opioid use, focussing on symptom and quality of life (QoL) improvements after 12 months of ASV. These comorbid patients had severe CSA that was effectively treated by ASV. Despite a high dropout rate, significant improvements in sleepiness and disease-related QoL were seen, but not in general QoL. Whilst encouraging, this study has several flaws (opioid use data were not collected, lack of sleep data to allow proper cohort phenotyping, and no objective measures of sleepiness) that could be addressed in a prospective trial.

Reference: J Clin Sleep Med. 2025;21(7):1227–32
Abstract

References: 1. MOUNJARO® Approved Product Information. **2.** Malhotra A *et al. N Engl J Med* 2024; 391(13): 1193–205 (including supplement). **3.** Chang JL *et al. Int Forum Allergy Rhinol* 2023; 13(7): 1061–482.

Subclinical augmentation in relation to previous dopaminergic treatment in patients with restless legs syndrome

Authors: Garcia-Borreguero D et al.

Summary: This post hoc analysis of two randomised, placebo-controlled, crossover trials investigated whether prior long-term dopaminergic treatment affects future responses to dopaminergic and non-dopaminergic drugs in patients with restless legs syndrome (RLS). In the two trials, patients with RLS underwent a 2-week washout before receiving active treatment (suvorexant 10–20mg or dipyridamole 200–300mg) or placebo for 2 weeks, followed by crossover to the alternate arm. None of the patients met diagnostic criteria for augmentation. Responses in patients who had previously received dopamine agonist (DA) therapy (DA-pretreated patients) were compared with those in patients who were DA-naïve. Overall, 28 patients participated in the dipyridamole study (ten were DA-pretreated and 18 were DA-naïve) and 40 participated in the suvorexant study (nine were DA-pretreated and 31 were DA-naïve group). Both suvorexant and dipyridamole had greater efficacy in DA-naïve patients than in DA-pretreated patients.

Comment: Dopamine agonists have been the first-line treatment for RLS for several decades. Although effective initially, with continued use there is often a gradual loss of efficacy, and eventually augmentation may occur, with worse RLS symptoms than before treatment initiation. This study was a post hoc analysis of two previous trials of dipyridamole (an adenosine transport inhibitor) and suvorexant (an orexin receptor antagonist) for RLS. Both agents have been previously shown to be effective for RLS, and neither act via dopamine pathways. Patients with augmentation were excluded. Subjective and objective improvements were seen with both treatments, but were greater in DA-naïve patients than in those who had previously received DA. This suggests that a negative effect of DA occurs well before augmentation develops, however longer trials are required to assess whether treatment responses improve over time in previously DA-treated patients.

Reference: CNS Drugs 2025;39(8):779–93
Abstract

Sleep tracking and sleep hygiene counseling improve fatigue in pediatric patients with inflammatory bowel disease

Authors: Kuzoian S et al.

Summary: This single-centre randomised controlled trial investigated whether sleep tracking and sleep hygiene counselling can reduce fatigue in children and adolescents with IBD. Forty-three patients aged 12–20 years with IBD and fatigue due to impaired sleep (Pediatric Quality of Life-Multidimensional Fatigue Scale [PedsQL-MDFS] score <60) were randomised 1:1 into two intervention groups. Both groups were asked to track their sleep for 2 weeks using a standardised sleep log, while Group B also had in-person sleep hygiene counselling. The PedsQL-MDFS Sleep/Rest Fatigue score improved significantly in both groups after 2 weeks, and sleep hygiene counselling significantly increased the number of patients who turned off their electronic screens 30 min before bedtime.

Comment: Impaired sleep and fatigue are common complaints in patients with IBD and are increased compared with healthy controls. Mounting evidence suggests sleep and inflammation are linked, with inflammation disrupting sleep, and poor sleep quality increasing the severity of inflammation and risk of IBD relapse. This prospective trial sought to examine whether the simple interventions of sleep tracking (via a written sleep diary) and sleep hygiene advice (one session, with written instructions) could improve sleep behaviour and reduce fatigue in paediatric patients with IBD. Exclusion criteria included current active gastrointestinal symptoms that could disrupt sleep, steroid use within the last fortnight, and a previously diagnosed sleep disorder. Although a single-centre study with small patient numbers, they were able to show self-reported improvements in fatigue with these simple interventions at 2 weeks. Of concern, only around a third of patients were achieving the recommended amount of sleep for their age.

Reference: J Pediatr Gastroenterol Nutr. 2025;81(1):62–8
Abstract

Long-term welfare consequences of sleep apnea in 20-64-year-olds – influence of gender

Authors: Jennum P et al.

Summary: This nationwide cohort study analysed data from the Danish National Patient Registry and other public databases to evaluate the influence of sex on the long-term welfare of patients with OSA. A total of 75,025 male and female patients aged 20–64 years with OSA were matched 1:4 with 300,744 healthy controls by age, sex, marital status, and community location. Patients with OSA had significantly higher morbidity, mortality, and health costs than healthy controls, but lower educational level and retirement age. These patterns were seen up to 15 years before diagnosis, and became more pronounced after diagnosis and management. Females had higher morbidity and mortality rates and welfare costs than males before and after diagnosis. The net costs for males versus females were 4217 vs 8259 €/year before diagnosis and 8749 vs 13,730 €/year after diagnosis.

Comment: This 'big data' nationwide cohort study from Denmark provides concerning insights into the enormous impact of OSA on individuals and on society. Using the Danish National Patient Registry and other national registers, they identified working-aged people with a diagnosis of OSA and compared them with a group of 1:4 matched non-OSA controls. The same authors have previously studied the impact of OSA in children and older adults. Health care costs were analysed in detail (primary healthcare visits, hospital admissions, outpatient and psychiatric services, medication costs) as were social demographics (educational level, employment, income, welfare). Overall, patients with OSA had 2–3 times the healthcare costs of non-OSA people, lower employment and lower educational levels. Women faired poorly compared with men, with higher morbidity, mortality and social welfare costs. This data underscores the importance of early interventions addressing health inequities.

Reference: Sleep 2025;48(7):zsaf057
Abstract

Independent commentary by Dr Elizabeth Veitch, MBBS FRACP

Dr Elizabeth Veitch is Head of Respiratory and Sleep Medicine at Concord General Hospital in Sydney. She has broad clinical practice and interests, with particular focus on airways diseases, interstitial lung diseases, pulmonary embolism and respiratory failure in neuromuscular disease. Over the last 20 years she has been a principal investigator on multiple international, multi-centre trials of novel medications for COPD, bronchiectasis and interstitial lung diseases.

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Waking up to Australia's sleep health: A consensus statement from the Network of Early Career Sleep Researchers in Training (NEST) council of the Australasian Sleep Association

Authors: Crowther ME et al.

Summary: The NEST is a council of the Australasian Sleep Association (ASA) that represents students and early-career researchers. They have released a consensus statement that presents practical considerations for advancing Australia's national sleep health agenda. Proposed goals include: 1) the development of a national sleep health and well-being strategy; 2) a nationwide sleep health awareness campaign; 3) education of healthcare practitioners in sleep medicine and sleep health; and 4) funding for sleep research.

Comment: We spend up to a third of our life sleeping and the importance of sleep for health is undeniable, yet this area has received much less attention than the other pillars of health, nutrition and physical activity. Furthermore, inadequate sleep is enormously costly for Australia, estimated at $75 billion in 2019–2022. This statement, by an ASA council and endorsed as an official ASA statement, was made in response to a Parliamentary Inquiry into Sleep Health Awareness, the Bedtime Reading Report (tabled in April 2019) and the Government's response (tabled in August 2023). It focusses on some important goals, such as society and healthcare sleep education, equity of sleep healthcare access and research funding, but does not comment on other recommendations of the Bedtime Reading Report, including increased monitoring of the CPAP industry and that the government investigate ways to divide "Respiratory and Sleep Medicine" into separate specialties under AHPRA.

Reference: Sleep 2025;48(7):zsaf100
Abstract

Implementation of European national driving regulations for obstructive sleep apnoea: Challenges and recommendations

Authors: McNicholas WT et al., for the Study Collaborators in the Assembly of National Sleep Societies and other National Representatives

Summary: The European Commission has introduced a legal directive restricting driving in patients with moderate to severe OSA and sleepiness, unless effectively treated. This study evaluated the implementation of the directive in European Union (EU) member and non-member states. Data were obtained from 25 out of 27 EU member states and all eight non-member states. All EU members had introduced the directive largely unchanged into national regulations (some countries applied stricter criteria), but only five non-member states had driving regulations for OSA. Most of the countries reported problems with implementation of the regulations.

Comment: Patients with untreated OSA have a higher rate of motor vehicle accidents, generally considered to be 2–3 times the population risk, and treatment with nocturnal CPAP reduces this risk. In 2015 the EU released a directive regarding driving fitness in OSA patients, which stated that those with moderate or severe OSA (AHI ≥15/h of sleep) and daytime sleepiness should be restricted from driving until the disorder was effectively treated. There were many 'holes' in this directive, including no guidance on how sleepiness should be assessed, what level of sleepiness precludes driving, nor specific treatment criteria to allow driving resumption. Incorporation of the directive into national driving regulations was universal in responding EU countries (25 out of 27), but surprisingly, two of these and the UK opted for a more rigid AHI of >5 events/h. This article highlights the ongoing uncertainty of how to assess driving safety plus the heterogeneity of existing regulations.

Reference: Eur Respir J. 2025;66(1):2402484
Abstract